AMENDMENTS TO THE DRAWINGS

Please replace the Drawings for Figures 1-3 and 5 of the Application with the attached Replacement Sheets (4 pages).

REMARKS

In this amendment, claims 1-11 and 13-18 are amended and claims 19-20 are new. Thus, after entry of this Amendment, claims 1-20 are all the claims pending in the application.

Claims 1-11 and 13-18 have been amended in form only to more clearly claim the invention, thereby facilitating examination. Further, claims 11, 13 and 14 have been re-written in independent form.

The recitation of "one of four HIV-1 subtypes" in claims 1 and 18 is supported by the specification, for example, by claim 11 which encompasses methods of distinguishing between 4 HIV-1 subtypes.

The term "nested PCR" as recited in amended claim 8, for example, is supported by the specification at page 13, line 5.

New claims 19 and 20 are supported by the specification at, for example, Figure 5, showing the use of primers of SEQ ID NOS: 20 and 28 for amplifying a polynucleotide of HIV-1 Subtype B.

The amendments to the claims are not intended to be narrowing.

No new matter has been added.

Claim for Foreign Priority

Applicants request that in the next correspondence the Examiner indicate whether the certified copies of the priority documents have been received from the International Bureau.

In addition, please find attached to this Amendment an English language translation of the priority documents (Japanese Application Nos: 1999-167736 and 2000-23581)

Response to Examiner's Requirement for Restriction

At page 2 of the Office Action, the Examiner restricts claims 1-18 into the following Groups:

> Group I, claims 1-17, drawn to methods of determining HIV-1 subtypes by amplifying a portion of the env gene of HIV-1.
>
> Group II, claim 18, drawn to a kit comprising primer pairs.

The Examiner requires that Applicants elect either Group I or Group II, and further, that Applicants elect a species for examination.

On May 30, 2003, a provisional election was made to prosecute the invention of Group I. This election was made with traverse. Further, regarding the election of species requirement, primers 10U and 11VB (SEQ ID NOS: 20 and 28) were elected for examination.

First, Applicants traverse the requirement for restriction as to claim 18, because the examination of claim 18 does not present an additional burden on the Office. That is, if the method of claim 1 is found allowable, the corresponding kits of claim 18 will almost certainly be allowable as well.

In addition, Applicants request that the Examiner expand the search to include the entire subject matter of claim 1, since the elected species has not found in the prior art. Applicants submit that the Examination of claims 13 and 17 does not present a further burden on the Office.

Response to Examiner's Objections to the Drawings

At page 4 of the Office Action, the Examiner objects to the Drawings because they do not contain a sequence identifier following the primer sequences. In addition, the Examiner contends that the application contains sequence disclosures that are not included in the Sequence Listing (Applicants presume that the Examiner is referring to Figures 1 and 2).

Attached to this Amendment are Replacement Sheets for the Drawings corresponding to Figures 1-3 and 5. Figures 1-3 and 5 have been revised to include the sequence identifiers as requested by the Examiner.

In addition, Applicants submit herewith a Substitute Sequence Listing along with a computer readable copy of the same, which include the sequences set forth in Figures 1 and 2, in addition to those sequences listed in the prior Sequence Listing filed December 14, 2001.

Applicants believe that this submission is fully in compliance with the Examiner's requirement, and accordingly, Applicants request that the Examiner's objections be withdrawn.

Response to Claim Rejections Under 35 USC § 112, Second Paragraph

At page 4 of the Office Action, claims 7 and 9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner contends that the recitations of "(primer 1)," "(nucleotide sequence 1)," "(primer 2)" and "(nucleotide sequence 2)" render claims 7 and 9 indefinite because it is unclear how these parentheticals further limit the claim.

Amended claims 7 and 9 do not identity terms through parentheticals. Accordingly, Applicants request that this rejection be withdrawn.

Claim Rejections Under 35 USC § 103

At page 6 of the Office Action, claims 1-10, 12, and 14-16 are rejected under 35 U.S.C. § 103(a) as being obvious over Barbosa *et al.* (*Tranfus. Sci.* Vol. 19, No. 1, pages 39-43, 1998) in view of: U.S. Patent Application Publication 2002/0106639 to Wang *et al.* (August 2002); Korber, Human Retroviruses and AIDS (1992 and 1997); and US Patent 5,595,874 to Hogan (1997).

The Examiner contends that Barbosa teaches a method of distinguishing between HIV-1 subtypes (A to I) using PCR and heteroduplex mobility, and teaches PCR amplification of HIV-1 *env* gene regions. The Examiner further contends that Barbosa teaches that the method is able to distinguish between individual strains and may also provide reliable information for phylogenetic analysis. The Examiner contends that Barbosa teaches using the C2 and C3 regions of the *env* gene. The Examiner notes that positions 7001-7020 are the same regions identified by Delwart *et al.*, who, according to the Examiner, also teaches SEQ ID NO: 20 of the present application.

The Examiner admits that Barbosa does not specifically teach a method for determining HIV-1 subtypes that uses different pairs of primers for different HIV-1 subtypes.

However, the Examiner contends that Wang teaches methods for determining PCV subtypes using a multiplex PCR assay based on a comparison alignment of PCVI and II. The Examiner contends that Wang designed two primers to identify PCV group-specific sequences and strain-specific sequences.

Further, the Examiner contends that both Korber 1992 and Korber 1997 teach HIV genomic sequences of the *env* gene from various subtypes, and provide "consensus" sequences for Subtypes A, B, C, D, E, O.

The Examiner contends that Hogan teaches a method for designing specific oligonucleotide probes based on nucleotide sequences which differ between the target organism and its phylogenetically closest relatives.

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill at the time the invention was made, to modify the methods of Barbosa, directed to distinguishing between HIV-1 subtypes, with the method of Wang (which uses primers specific to particular PCV subtypes based on comparative analysis), and based on the information disclosed by Delwart (HIV genomic sequences) and Hogan (methods for primer design).

Response to Section 103 Rejection

Applicants respectfully request reconsideration of this rejection, as the references cited by the Examiner provide objective evidence of non-obviousness. As the Examiner is aware, objective evidence of non-obviousness must be considered where present, as set forth by MPEP § 2141.

Specifically, Barbosa, Delwart, and Hahn provide evidence that there was a long-felt need for a non-labor intensive method of determining HIV-1 subtype or genetic makeup of an HIV-1 population, and that prior to the effective filing date of this application, there was a failure of others to provide such a method utilizing PCR.

First, Barbosa states at page 39 that since serological tests are frequently inconclusive, methods to distinguish HIV-1 subtypes are needed. Second, Hahn states at column 3, lines 6-10

that "[g]iven the unkown impact of genetic variation on correlates of immune protection, subtype specific reagents are critically needed for phylogenetic, immunological, and biological studies." And third, Delwart at page 348 describes the complexity in determining the genetic makeup of an HIV-1 population using PCR, and particularly with the *env* gene. Delwart further proposes a DNA heteroduplex assay to estimate the degree of genetic divergence between two isolates.

Thus, Applicants submit that the present invention is not obvious over the cited art, because, although non-labor intensive methods of determining HIV-1 subtype were critically needed, and given that PCR (a non-labor intensive method) was a well-known technique as of the priority date of this application, no reliable method for determining HIV-1 subtype using PCR had been successful.

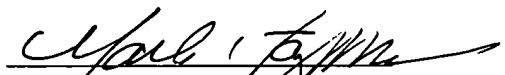
Accordingly, the present claims are not obvious over the cited art because the cited art provides objective evidence of a long-felt need for, and objective evidence of the failure of others to provide, the present invention. Applicants respectfully request that the section 103 rejection be withdrawn.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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